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Research Article

Nutrition, Gut Microbiota, and Epigenetics in the First 1,000 Days: Implications for Clinical Nutrition

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Abstract

Introduction: The first 1,000 days of life (from conception to 2 years) represent a critical window for biological programming. During this period, the interplay between maternal-infant nutrition, gut microbiota, and epigenetic mechanisms exerts a decisive influence on future health.

Objective: To critically analyze the available evidence regarding the role of nutrition and microbiota during the first 1,000 days and their interaction with epigenetics, as well as the clinical and public health implications.

Methods: A narrative review of the literature published between 2015 and 2025 was conducted in PubMed, Scopus, and Web of Science. Included studies comprised clinical trials, cohort studies, and mechanistic research evaluating microbiota composition, microbial metabolites, and epigenetic markers in pregnant women, infants, and children under 24 months.

Results: Fifty-eight studies were analyzed. Exclusive breastfeeding promoted colonization by *Bifidobacterium longum subsp. infantis*, leading to increased production of short-chain fatty acids (SCFAs) that modulate DNA methylation and histone acetylation. Vaginal delivery and maternal-infant diets rich in fiber, folate, choline, and vitamin B12 were associated with protective epigenomic profiles. Conversely, elective cesarean delivery, early antibiotic exposure, and high consumption of ultra-processed foods were linked to dysbiosis and adverse epigenetic patterns.

Conclusion: The interaction between nutrition, microbiota, and epigenetics in the first 1,000 days represents a unique opportunity for cost-effective public health interventions aimed at optimizing long-term health outcomes.

Keywords: *First 1,000 Days; Gut Microbiota; Epigenetics; Breastfeeding; Infant Nutrition*

Abbreviations

AhR: Aryl Hydrocarbon Receptor; BMI: Body Mass Index; B12: Vitamin B12 (Cobalamin); CVD: Cardiovascular Disease; DNA: Deoxyribonucleic Acid; DNMTs: DNA Methyltransferases; DOHaD: Developmental Origins of Health and Disease; DXA: Dual-Energy X-ray Absorptiometry; FXR: Farnesoid X Receptor; GI: Gastrointestinal; GDM: Gestational Diabetes Mellitus; GPCRs: G Protein-Coupled

Receptors; HDACs: Histone Deacetylases; HMOs: Human Milk Oligosaccharides; IGF2: Insulin-Like Growth Factor 2; IgA: Immunoglobulin A; IL-22: Interleukin-22; lncRNAs: Long Non-Coding RNAs; LEP: Leptin Gene; microRNAs (miRNAs): Small Non-Coding RNAs that Regulate Gene Expression; PAMPs: Pathogen-Associated Molecular Patterns; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RXRA: Retinoid X Receptor Alpha; SCFAs: Short-Chain Fatty Acids; TMA/TMAO: Trimethylamine/Trimethylamine N-Oxide; Tregs: Regulatory T Cells; TGR5: G Protein-Coupled Bile Acid Receptor 1

Introduction

The Developmental Origins of Health and Disease (DOHaD) hypothesis proposes that early-life exposures program disease risk through persistent mechanisms, including epigenetic modifications [1]. In parallel, the gut microbiota has been consolidated as a key regulator of immunity, metabolism, and neurodevelopment during the first 1,000 days [2-7]. This convergence highlights the relevance of maternal-infant nutrition and microbial colonization as determinants of lifelong health.

Conceptual framework (Executive synthesis) (See figure 1)

- **The first 1,000 days:** From conception to 24 months, this is the period of greatest biological plasticity, programming lifelong risks and protections (DOHaD) [1].
- **Gut microbiota:** A dynamic ecosystem that, in healthy infants, shifts from low diversity to *Bifidobacterium*-dominated communities during breastfeeding, then toward greater diversity with complementary feeding. It shapes immune education, energy metabolism, and barrier maturation [2,3].
- **Epigenetics:** Includes DNA methylation, histone modifications (acetylation/methylation), and non-coding RNAs (microRNAs, lncRNAs). These mechanisms are modulated by maternal-infant diet and microbial metabolites (e.g., SCFAs such as butyrate/propionate/acetate, tryptophan-derived indoles, bile acids, and one-carbon donors such as folate, choline, and B12) [1].

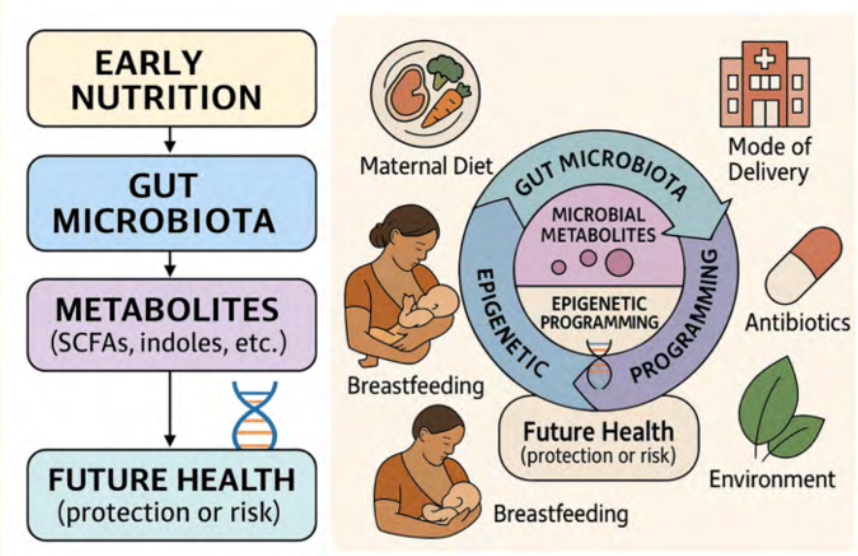

Figure 1: *Epigenetics, microbiota, and future health: the influence of early nutrition.*

Source: Authors' own work.

The figure shows the Relationship between early nutrition, gut microbiota, and future health. Maternal diet, breastfeeding, mode of delivery, antibiotic exposure, and environmental factors shape the microbiota. Microbial metabolites (e.g. short-chain fatty acids, indoles) mediate epigenetic programming, influencing long-term health outcomes as either risk or protection.

The first 1,000 days of life, from conception to two years of age, represent a critical window of human development characterized by remarkable biological plasticity. During this period, the foundations are established for immune system maturation, somatic growth, metabolic programming, and neurocognitive development. Several studies have demonstrated that early stimuli and exposures exert lasting effects through programming mechanisms, modulating the risk of chronic diseases throughout the life course, including obesity, type 2 diabetes, allergies, asthma, cardiovascular disease, and neuropsychiatric disorders [1,2]. This concept is supported by the Developmental Origins of Health and Disease (DOHaD) hypothesis [1] which has broadened the vision of prevention to very early stages of life.

In this context, the gut microbiota has emerged as a fundamental player in the first 1,000 days. The process of intestinal colonization begins at birth and is influenced by factors such as mode of delivery, antibiotic exposure, and feeding practices [3-7]. During the first months of life, breast milk-rich in oligosaccharides, secretory immunoglobulin A, lactoferrin, microRNAs, and immune cells-promotes the growth of *Bifidobacterium longum* subsp. *infantis* and other beneficial commensal bacteria [8-11]. These communities produce metabolites such as short-chain fatty acids (butyrate, propionate, acetate), tryptophan-derived indoles, and secondary bile acids, which exert regulatory effects on inflammation, metabolism, and intestinal barrier integrity [13-19]. The transition to complementary feeding diversifies the microbiota and consolidates its metabolic and protective functions [2-20].

Epigenetics, in turn, encompasses the set of mechanisms that regulate gene expression without altering the DNA sequence. These include DNA methylation, histone modifications (acetylation, methylation, phosphorylation), and the action of non-coding RNAs (microRNAs, lncRNAs). These programs allow environmental signals, including nutrition and microbial metabolites, to modulate gene activity in a dynamic and reversible manner [1-21]. Paradigmatic examples include the persistent hypomethylation of the *IGF2* gene in individuals exposed to the Dutch famine during gestation [22]. The methylation of *RXRA* associated with childhood adiposity [23] and epigenetic changes linked to maternal intake of folate, choline, and vitamin B12 at conception and during pregnancy [24,25]. The microbiota-epigenetic interaction is bidirectional: microbial metabolites can act as histone deacetylase inhibitors or as ligands for nuclear receptors [15-19] while epigenetic marks determine the host's response to bacterial colonization and diet [21].

The integration of the concepts of the first 1,000 days, microbiota, and epigenetics naturally aligns with the One Health framework. This paradigm recognizes the interdependence between human health, animal health, and the environment. Early microbial colonization is influenced not only by individual clinical factors but also by environmental exposure, food quality, water safety, and interaction with animals [2,5,6]. Rational use of antibiotics, in both human and veterinary medicine, is a critical element, as antimicrobial resistance affects microbial dynamics and poses shared risks for humans and animals [7,8]. Likewise, maternal and infant diets depend on sustainable food systems that integrate agriculture, livestock, and environmental stewardship [20].

Consequently, the study of epigenetic programming and the establishment of the microbiota in the first 1,000 days cannot be limited to an individual clinical perspective, but requires an interdisciplinary and global approach that incorporates the dimensions of One Health. Only through this comprehensive perspective is it possible to understand the biological, social, and environmental determinants of health in early childhood and to design cost-effective strategies to improve the health of future generations [2,14,16].

Materials and Methods

Search strategy

The literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science databases between January 2015 and May 2025. Combinations of DeCS/MeSH terms were used in both Spanish and English, including: "first 1000 days", "gut microbiota", "epigenetics", "breastfeeding", "cesarean section", "short-chain fatty acids", "maternal nutrition", and "epigenesis, genetic".

Inclusion criteria

- Human studies (pregnant women, infants, and children <24 months).
- Clinical trials, cohort studies, case-control studies, systematic reviews, and high-quality narrative reviews.
- Mechanistic and translational research on microbial metabolites (short-chain fatty acids, indoles, bile acids) and epigenetic mechanisms (DNA methylation, histone modifications, microRNAs).

Exclusion criteria

- Animal studies without direct clinical applicability.
- Studies lacking epigenetic, metabolic, or immunological outcomes.
- Duplicate articles or reports with redundant information.

Study selection and analysis

The initial search identified 612 articles. After removal of duplicates (134), 478 records remained. Of these, 325 were excluded for not meeting inclusion criteria after title and abstract screening. A total of 153 full-text articles were assessed, of which 95 were excluded for lack of clinical data or relevance. Ultimately, 58 studies were included in the narrative analysis: 22 systematic and narrative reviews, 14 clinical trials, 13 cohort studies, and 9 translational investigations with clinical applicability (See figure 2).

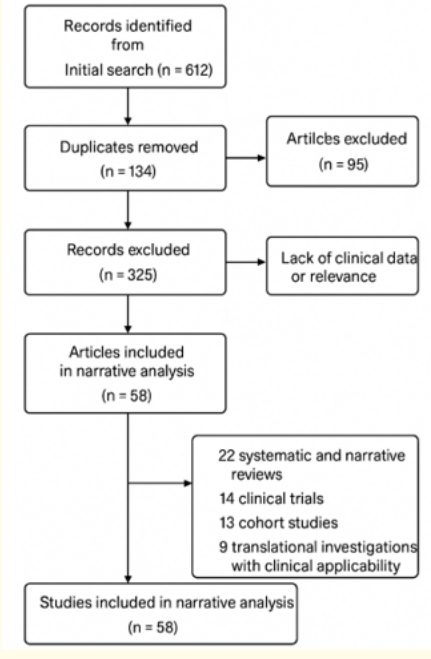

Figure 2: *PRISMA flow diagram.*

Source: Authors' own work.

Methodological approach

The selected studies were organized into five thematic domains:

1. Early microbial colonization and determining factors.
2. Breastfeeding, human milk oligosaccharides (HMOs), and *Bifidobacterium infantis*.
3. Influence of delivery mode and antibiotics on the microbiota.
4. Role of maternal-infant diet in epigenetic regulation.
5. Microbial metabolites and associated epigenetic mechanisms.

The analysis integrated clinical and molecular findings within a translational framework, emphasizing practical implications for clinical nutrition and their relationship with the conceptual framework of One Health.

Given the nutritional focus of this review, specific attention was directed to dietary exposures and feeding practices during the first 1,000 days. Studies were coded for nutritional variables including maternal macronutrient and micronutrient intake (folate, choline, vitamin B12, and polyphenols), breastfeeding and human milk composition, formula supplementation (e.g., HMOs, probiotics), and complementary feeding quality (fiber, protein, and sugar sources). This approach ensured that nutrition-related mechanisms were consistently analyzed in relation to microbiota composition and epigenetic modulation [9-14,20-26,29-31,33-36].

Results

Early microbial colonization

Of the 58 studies included, most agreed that intestinal colonization begins immediately at birth, with distinct profiles depending on the mode of delivery. Vaginally delivered infants showed higher abundance of *Bacteroides* and *Lactobacillus* [3,4] whereas cesarean delivery was associated with opportunistic species such as *Clostridium difficile* [5,6]. These patterns were linked to differences in immune maturation during the first year of life [7,8].

During this first year, the infant microbiome progresses toward greater diversity and stability, with metabolic functions maturing in a predictable trajectory [3,4]. Age, geographical location, and lifestyle factors also exert significant influence [4].

Phase	Biological milestones	Determinant exposures	Predominant microbiota	Key epigenetic signals	Clinical implications	Key references
Gestation	Organogenesis; immune and metabolic maturation	Maternal diet; BMI; gestational diabetes; tobacco; stress; drugs; probiotics	Maternal influence via metabolites and transplacental factors	Methyl-donor nutrients (folate, choline, vitamin B12); maternal cortisol; placental microRNAs	Programming of fetal growth, insulin sensitivity, adiposity, and atopic risk	1, 20-23, 26, 29-30, 35-36
Birth	Initial microbial colonization	Vaginal vs cesarean delivery; intrapartum antibiotics	Vaginal: *Lactobacillus*, *Bacteroides* dominance; Cesarean: increased *Staphylococcus*, *Enterococcus* and opportunists	Immune "imprinting"; altered DNA methylation of immune genes	↑ Risk of asthma, atopy, and obesity associated with cesarean birth or perinatal antibiotic exposure	4-7, 24, 29-30, 37

0 - 6 months	Exclusive breastfeeding phase	Breast milk components (HMOs, IgA, lactoferrin); antibiotic exposure; environment	*Bifidobacterium longum subsp. infantis*, *B. longum*, *Lactobacillus* predominate	Butyrate/acetate (↓ HDAC activity); milk microRNAs; methylation of metabolic and immune genes	↓ GI and respiratory infections; improved growth, neurodevelopment, and immune tolerance	3, 9-14, 15-17, 24-25, 29-33
6 - 24 months	Complementary feeding and microbiome diversification	Dietary fiber quality; protein and sugar intake; environmental exposures (pets, day-care)	Increased diversity; rise in *Firmicutes* and *Bacteroidetes*; maturation of SCFA-producing taxa	SCFA and indole signaling; bile-acid crosstalk; tissue-specific methylation changes	Influences BMI trajectory, atopic risk, and cognitive function	3, 15, 18-19, 24, 30-31, 33-34, 36

Table 1: *Chronology of the human microbiome and epigenetic modulation during the first 1000 days.*

Source: Authors' elaboration.

Breastfeeding and HMOs

Exclusive breastfeeding was consistently associated with predominance of *Bifidobacterium longum subsp. Infantis* [9,12] a key species for fermentation of human milk oligosaccharides (HMOs) [8,10]. In clinical trials, this colonization correlated with higher short-chain fatty acid (SCFA) production [13-15] and reduction of intestinal inflammation markers [11,12].

Antibiotic use and cesarean delivery

Cesarean section disrupts maternal strain transmission (notably *Bacteroides*) and is associated with increased colonization by opportunists and resistance genes, with effects lasting for months [5,6]. Antibiotics administered in early life reduced microbial diversity and depleted *Bifidobacterium* [7,8]. Cohort studies showed these alterations could persist up to two years, increasing the risk of overweight and allergic diseases [6,25]. Perinatal diet and antibiotics also shaped microbial succession [7] while a randomized neonatal sepsis trial demonstrated that broad-spectrum antibiotics reconfigured both microbiota and resistome [8]. The resistome represents the full repertoire of antimicrobial resistance genes in humans, animals, and the environment, serving as a reservoir that can spread through horizontal gene transfer. Recent studies (2025) have shown that resistance gene flow occurs across One Health sectors in regions like China, and that global soil resistomes are strongly influenced by environmental drivers, underscoring their ubiquity and ecological impact. These findings highlight how antibiotic use in healthcare, agriculture, and environmental contexts accelerates the dissemination of resistance genes. Understanding and monitoring the resistome is therefore critical for designing strategies to curb antimicrobial resistance and protect global health [27,28].

Maternal diet and epigenetics

Maternal nutritional status during conception and pregnancy influences fetal epigenetic programming through DNA methylation of genes regulating growth and metabolism. Evidence from famine and dietary restriction studies indicates that overall nutrient and energy availability, rather than specific vitamin intake, can modify methylation at critical loci. For example, prenatal exposure to famine during early gestation has been associated with hypomethylation of insulin-like growth factor 2 (IGF2), possibly reflecting limited methyl-donor

availability [20]. Similarly, variations in maternal carbohydrate composition and energy balance have been linked to hypermethylation of retinoid X receptor-α (RXRA)and endothelial nitric-oxide synthase (eNOS) promoters, and hypomethylation of superoxide dismutase 1 (SOD1), patterns associated with later adiposity and body-fat distribution in offspring [21]. In contrast, maternal diets rich in ultra-processed foods have been linked to adverse epigenetic modifications and systemic inflammation [13,26].

Beyond one-carbon metabolism, emerging evidence links the overall quality of maternal diet - particularly the ratio of unprocessed to ultra-processed foods, fiber intake, and fatty acid composition - to microbial diversity and inflammatory tone. Diets high in fiber and polyphenols enhance the production of short-chain fatty acids (SCFAs) such as butyrate and propionate, which function as histone deacetylase inhibitors and anti-inflammatory metabolites [15-19,29-31,34,36]. Conversely, energy-dense, ultra-processed diets rich in saturated fats and refined sugars are associated with dysbiosis, systemic inflammation, and unfavorable DNA methylation profiles affecting genes involved in insulin sensitivity and adiposity regulation [13,20-26,29-31,35,36]. These nutritional dimensions represent modifiable determinants of fetal and infant epigenetic programming.

Microbial metabolites and epigenetic mechanisms

SCFAs-acetate, propionate, butyrate-derived from fiber and HMO fermentation act on GPCRs, serve as energy substrates, and inhibit histone deacetylases (HDACs), thereby altering immunometabolic gene expression) [15-17]. Indole metabolites of tryptophan activate AhR and induce IL-22, a mucosal homeostasis regulator [18] while secondary bile acids modulate FXR/TGR5 pathways that influence host metabolism [19].

Metabolite	Origin	Main target	Epigenetic effect	Functional consequence	Key references
Butyrate / Propionate	Fermentation of dietary fibers by *Bifidobacterium* and *Lactobacillus* spp.	HDACs (histone deacetylases)	HDAC inhibition → ↑ histone acetylation	↑ Regulatory T cells (Tregs); anti-inflammatory activity; improved epithelial barrier integrity	15-17, 29-31
Indoles (AhR ligands)	Microbial tryptophan catabolism	Nuclear aryl hydrocarbon receptor (AhR)	Activation of AhR signaling; modulation of microRNAs and IL-22 transcription	Maintenance of mucosal homeostasis and epithelial regeneration	18, 30-31, 36
Secondary bile acids	Bacterial conversion of primary bile acids	FXR (farnesoid X receptor) / TGR5 (G-protein-coupled bile acid receptor 1)	Chromatin and co-activator modulation	Regulation of glucose and lipid metabolism; control of inflammatory tone	19, 30-31
Folate / Choline / Vitamin B12	Dietary intake plus microbial synthesis	DNMTs (DNA methyltransferases)	Altered DNA methylation in growth and metabolic genes	Long-term programming of metabolism, growth, and insulin sensitivity	20-23, 26, 29-31, 35-36

TMA / TMAO (trimethylamine N-oxide)	Microbial metabolism of choline and carnitine	Hepatic pathways and FMO3-dependent signaling	Indirect modulation of DNA and histone methylation (limited evidence in infants)	Potential links to cardiometabolic risk and oxidative stress	29-31, 34, 36

Table 2: *Epigenetic mechanisms modulated by the microbiota.*

Source: Authors' elaboration.

Human evidence of epigenetic programming

"Natural experiments" and maternal nutrition studies link gestational exposures with metabolic gene methylation. The Dutch Hunger Winter was associated with persistent IGF2 hypomethylation decades later [20,22]. The ALSPAC study (UK) showed RXRA promoter methylation in cord blood correlated with childhood adiposity by DXA at 6 and 9 years [21].

In Gambia, epiallele methylation varied by season of conception, reflecting dietary folate and methionine availability [23]. These metastable epialleles act as "epigenetic memories" of the periconceptional environment. Longitudinal European and Asian cohorts confirmed that early epigenetic changes persisted into adolescence and adulthood, influencing cardiometabolic risk [24,25].

Similar findings were reported in the Philippines and China, where maternal one-carbon nutrient intake associated with adolescent obesity and insulin resistance [25]. In India, the Pune Maternal Nutrition Study showed differential methylation of glucose homeostasis genes at birth predicted insulin resistance and adiposity during adolescence [25,26].

Clinical and public health implications

1. Promote vaginal delivery when safe and limit non-indicated cesareans, given their impact on microbial transfer [5,6].
2. Optimize antibiotic indications and duration in pregnant women and neonates [7,8].
3. Encourage exclusive breastfeeding for the first 6 months, continuing through the second semester, for well-documented individual and population-level benefits [25].
4. Ensure adequate maternal intake of folate, choline, B12, methionine, and other one-carbon donors; promote fiber and phytonutrients to support favorable microbial metabolites [15,23].
5. In selected cases, consider supplementation with specific HMOs and/or rational probiotics (e.g. *B. infantis* in breastfed infants) [9,12,14].

Nutritional aspect	Effect on gut microbiota	Epigenetic mechanisms	Long-term clinical consequences	Key references
Maternal nutrition (preconception and gestation)	Shapes maternal microbiota composition and vertical transmission to the fetus and neonate	DNA methylation, histone modifications, and placental microRNAs influenced by folate, B12, and choline status	Offspring risk of obesity, insulin resistance, and hypertension determined by intrauterine programming	1, 20-23, 26, 29-31, 35-36

Mode of delivery (vaginal vs cesarean)	Vaginal delivery favors *Lactobacillus* and *Bifidobacterium*; cesarean favors opportunistic and environmental taxa	Indirect influence through differences in bacterial metabolites and immune imprinting	Increased risk of atopy, asthma, and obesity after cesarean birth	4-7, 24, 29-31, 37
Breastfeeding	Human milk oligosaccharides (HMOs) promote *Bifidobacterium* growth; breast milk transfers commensal bacteria and immune factors	microRNAs, immunomodulatory peptides, and butyrate increase histone acetylation and regulate gene expression	Protection against infections, obesity, and autoimmune diseases	3, 9-14, 15-17, 24-25, 29-33
Early antibiotic exposure	Dysbiosis; reduction of commensal diversity and expansion of resistome	Altered transcription of inflammatory and metabolic genes; changes in histone acetylation patterns	Greater risk of allergic disease, asthma, and excess weight	7-8, 24, 29-31
Complementary feeding (timely and adequate)	Promotes diversification of the microbiota and establishment of SCFA-producing taxa	SCFAs (acetate, propionate, butyrate) regulate DNA methylation and histone acetylation of immune and metabolic genes	Prevention of obesity and metabolic diseases; improved immune tolerance	3, 15-19, 24, 29-31, 33-34, 36
Maternal and child diets rich in fiber and polyphenols	Stimulate beneficial *Firmicutes* and *Bacteroidetes*; increase SCFA and indole production	SCFAs act as HDAC inhibitors; polyphenols modulate microRNAs and antioxidant pathways	Lower risk of metabolic syndrome, cardiovascular disease, and inflammation	15, 18-19, 29-31, 34, 36
Micronutrient deficiencies (folate, B12, vitamin D, iron, zinc)	Impair microbial metabolism and reduce beneficial species	Disruption of DNA methylation and hormone-related epigenetic regulation	Neurodevelopmental delay; increased susceptibility to chronic disease	20-23, 26, 29-31, 35-36

Table 3: *Early-life nutrition and its relationship with the gut microbiota and epigenetics.*

Source: Authors' elaboration.

Discussion

The findings of this review confirm that the first 1,000 days of life represent a critical window of biological programming, where maternal-infant nutrition, gut microbiota, and epigenetic mechanisms interact in complex ways [1,2] (See table 3). Evidence shows that the initial composition of the microbiota is shaped by the mode of delivery and early exposures such as antibiotics [5-8]. These alterations, by modifying species succession and microbial metabolite production, generate distinct trajectories of immune and metabolic maturation [3,4,7].

Breastfeeding emerges as a key strategy to promote optimal colonization. Human milk oligosaccharides (HMOs) support the growth of *Bifidobacterium longum subsp. Infantis* [9-11] which enhances the production of short-chain fatty acids (SCFAs: acetate, propionate, and butyrate) [13-15]. These metabolites not only nourish the intestinal epithelium but also function as epigenetic modulators through inhibition of histone deacetylases (HDACs) [16,17]. Additionally, tryptophan-derived indoles activate the aryl hydrocarbon receptor (AhR), promoting secretion of interleukin-22 (IL-22) and reinforcing mucosal homeostasis [18,19].

In parallel, human epigenetic studies demonstrate that maternal nutrition shapes fetal genome programming. Landmark cases such as the Dutch Hunger Winter, which resulted in persistent hypomethylation of the IGF2 gene, and seasonal variation in one-carbon donor intake in Gambia, which modified metastable epialleles, confirm the sensitivity of the fetal epigenome to nutritional inputs [22,23]. These findings underscore the need to ensure adequate maternal intake of folate, choline, and vitamin B12 during pregnancy [20,21,24,25].

The clinical implications are clear: promoting vaginal delivery when safe, restricting antibiotic use to strictly necessary indications, encouraging exclusive breastfeeding during the first six months, and optimizing maternal nutrition constitute cost-effective interventions to mitigate future health risks [6-9,25] (See table 4).

From a One Health perspective, the health of the early microbiome depends not only on individual factors but also on environmental and social determinants. Water quality, food safety, exposure to pollutants, and antibiotic use in veterinary medicine directly impact the human microbiome and antimicrobial resistance [2,5,7]. Thus, the integrated approach to early nutrition, microbiota, and epigenetics requires intersectoral public policies that bridge clinical medicine with environmental health and sustainable food production [26,27,28].

Finally, although the results demonstrate significant coherence, limitations remain. Most included studies were observational, with methodological heterogeneity and variability in epigenetic biomarkers assessed. Moreover, translational research integrating multi-omics data and long-term follow-up is still lacking [2,13]. Nevertheless, the convergence of clinical, molecular, and epidemiological evidence reinforces the relevance of this field as a priority for public health and clinical nutrition.

From a nutritional perspective, the convergence of diet, microbiota, and epigenetics provides actionable insights for clinical nutrition practice. Promoting balanced maternal diets rich in methyl-donor nutrients (folate, choline, B12), dietary fiber, and polyphenols can enhance beneficial microbial metabolite production and favorable methylation patterns [13,20-26,29-31,35,36]. During infancy, exclusive breastfeeding and timely, diverse complementary feeding support optimal microbial and epigenetic development [3,9-14,15-17,24,25,29-33]. These findings reinforce the central role of nutrition as both a biological driver and a public health tool for long-term disease prevention within the DOHaD framework [1,2,29-31,33-36].

Exposure	Effect on microbiota	Epigenetic link/ mechanism	Expected clinical impact	Strength of evidence	Key references
Breastfeeding	↑ *Bifidobacterium* and HMO pathways	SCFAs (↓ HDAC activity), milk microRNAs, choline-dependent methylation	↓ Infections; ↓ atopy; ↓ obesity; ↑ neurodevelopment	High	3, 9-17, 24-25, 29-33
Cesarean section	↓ *Bacteroides* early; skin-like colonization	Reduced "training" of PAMPs → impaired immune tolerance	↑ Risk of atopy, asthma, obesity (associative)	Moderate	4-7, 24, 29-31, 37

Early antibiotics	↓ Microbial diversity; persistent dysbiosis	↓ SCFAs; subclinical inflammation; altered histone acetylation	↑ Infections, atopy; possible ↑ obesity	Moderate	7-8, 24, 27-28, 29-31
Maternal diet rich in ultra-processed foods	Maternal dysbiosis; ↑ proinflammatory metabolites	DNA methylation in metabolic genes (LEP, IGF2); reduced methyl donors	↑ Risk of childhood adiposity and metabolic dysfunction	Moderate	13, 20-26, 29-31, 35-36
Probiotics/synbiotics (pregnancy/lactation)	↑ *Bifidobacterium*/*Lactobacillus*; improved maternal and infant microbiota	↑ SCFA production; ↑ Treg cell modulation	↓ Mastitis; possible ↓ infant eczema (modest effect)	Moderate	9-12, 14, 15-17, 29-31, 33
HMOs in formula	Approximates bifidogenic profile	↑ SCFAs; improved immune signaling	↓ GI infections; limited evidence for allergy prevention	Moderate	9-14, 29-31, 33
Pet/farm exposure	Greater environmental microbial diversity	Controlled endotoxin exposure promotes epigenetic tolerance	↓ Atopy risk through immune education	Moderate	2, 4, 5, 6, 24, 29-31
Tobacco/pollution	Dysbiosis; inflammation; altered microbial metabolites	Global DNA methylation changes; oxidative stress pathways	↑ Low birth weight, wheezing, altered neurodevelopment	High	20-23, 26, 29-31, 35-36

Table 4: *Maternal-infant exposures with greatest impact.*

Source: Authors' elaboration.

Integration of nutritional and epigenetic evidence

Epigenetic mechanisms represent a crucial interface between maternal nutrition and gene expression during fetal development.

The synthesis of the 58 studies included in this review highlights consistent epigenetic links between maternal nutrition, microbial colonization, and early developmental outcomes. One-carbon donors such as folate, vitamin B_{12}, choline, and betaine, together with long-chain polyunsaturated fatty acids, regulate methylation and expression of key genes involved in metabolic homeostasis-LEP (leptin), ADIPOQ (adiponectin), IGF2, H19, and PPARγ-which influence adipogenesis, insulin sensitivity, and fetal growth [38-43]. Meta-analyses and randomized controlled trials indicate that maternal adherence to a Mediterranean-type dietary pattern during pregnancy promotes protective methylation profiles in these metabolic and energy-regulating genes [40,42].

Postnatal determinants-including mode of delivery, antibiotic exposure, breastfeeding, and colonization with *Bifidobacterium infantis*-further modulate DNA-methylation and histone-acetylation patterns related to immune and metabolic maturation [45-52]. In parallel, human milk oligosaccharides (HMOs) act as epigenetically active prebiotics, influencing the microbiota composition and contributing to neurodevelopmental and behavioral outcomes [53-57].

Collectively, these findings provide a mechanistic framework connecting maternal and early-life nutrition with epigenetic regulation of growth, metabolism, and neurocognitive development. They reinforce the need for clinical nutrition strategies centered on optimizing maternal diet quality, prudent antibiotic use, and exclusive breastfeeding during the first 1,000 days to promote long-term health.

Conclusion

Early-life nutrition represents a critical window for shaping metabolic and neurodevelopmental health through epigenetic and microbial mechanisms. Maternal dietary quality-especially adequate intake of one-carbon nutrients (folate, vitamin B_{12}, choline, betaine) and polyunsaturated fatty acids-supports protective methylation patterns in key genes regulating growth, adipogenesis, and energy metabolism.

After birth, factors such as delivery mode, antibiotic exposure, breastfeeding, and the composition of the infant gut microbiota further influence these epigenetic trajectories. Promoting exclusive breastfeeding and prudent use of antibiotics helps preserve beneficial microbial colonization and gene-nutrient interactions essential for optimal development.

Integrating nutritional and epigenetic knowledge into perinatal care and clinical nutrition guidelines can strengthen preventive strategies aimed at reducing long-term risks of obesity, metabolic disorders, and neurodevelopmental impairment. The first 1,000 days thus remain a decisive period for interventions that promote lifelong health.

Bibliography

1. Waterland RA and Michels KB. "Epigenetic epidemiology of the developmental origins hypothesis". *Annual Review of Nutrition* 27 (2007): 363-388.
2. Robertson RC., *et al*. "The human microbiome and child growth - first 1000 days and beyond". *Trends in Microbiology* 27.2 (2019): 131-147.
3. Bäckhed F., *et al*. "Dynamics and stabilization of the human gut microbiome during the first year of life". *Cell Host and Microbe* 17.6 (2015): 852.
4. Yatsunenko T., *et al*. "Human gut microbiome viewed across age and geography". *Nature* 486.7402 (2012): 222-227.
5. Dominguez-Bello MG., *et al*. "Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns". *Proceedings of the National Academy of Sciences of the United States of America* 107.26 (2010): 11971-11975.
6. Shao Y., *et al*. "Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth". *Nature* 574.7776 (2019): 117-121.
7. Bokulich NA., *et al*. "Antibiotics, birth mode, and diet shape microbiome maturation during early life". *Science Translational Medicine* 8.343 (2016): 343ra82.
8. Reyman M., *et al*. "Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial". *Nature Communications* 13.1 (2022): 893.
9. Bode L. "Human milk oligosaccharides: every baby needs a sugar mama". *Glycobiology* 22.9 (2012): 1147-1162.
10. Sela DA., *et al*. "The genome sequence of *Bifidobacterium longum subsp. infantis* reveals adaptations for milk utilization within the infant microbiome". *Proceedings of the National Academy of Sciences of the United States of America* 105.48 (2008): 18964-18969.
11. Henrick BM., *et al*. "Colonization by *B. infantis* EVC001 modulates enteric inflammation in exclusively breastfed infants". *Pediatric Research* 86.6 (2019): 749-757.

12. Frese SA., *et al*. "Persistence of supplemented *Bifidobacterium longum subsp. infantis* EVC001 in breastfed infants". *mSphere* 2.6 (2017): e00501-17.

13. Wiciński M., *et al*. "Human milk oligosaccharides: Health benefits, potential applications in infant formulas, and pharmacology". *Nutrients* 12.1 (2020): 266.

14. Triantis V., *et al*. "Immunological effects of human milk oligosaccharides". *Frontiers in Pediatrics* 6 (2018): 190.

15. Koh A., *et al*. "From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites". *Cell* 165.6 (2016): 1332-1345.

16. Chang PV., *et al*. "The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition". *Proceedings of the National Academy of Sciences of the United States of America* 111.6 (2014): 2247-2252.

17. Siddiqui MT and Cresci GAM. "The immunomodulatory functions of butyrate". *Journal of Inflammation Research* 14 (2021): 6025-6041.

18. Zelante T., *et al*. "Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22". *Immunity* 39.2 (2013): 372-385.

19. Wahlström A., *et al*. "Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism". *Cell Metabolism* 24.1 (2016): 41-50.

20. Heijmans BT., *et al*. "Persistent epigenetic differences associated with prenatal exposure to famine in humans". *Proceedings of the National Academy of Sciences of the United States of America* 105.44 (2008): 17046-17049.

21. Godfrey KM., *et al*. "Epigenetic gene promoter methylation at birth is associated with child's later adiposity". *Diabetes* 60.5 (2011): 1528-1534.

22. Dominguez-Salas P., *et al*. "Maternal nutrition at conception modulates DNA methylation of human metastable epialleles". *Nature Communications* 5 (2014): 3746.

23. Joubert BR., *et al*. "Maternal plasma folate impacts differential DNA methylation in newborns". *Nature Communications* 7 (2016): 10577.

24. Milani C., *et al*. "First microbial colonizers of the human gut: Composition, activities, and health implications of the infant gut microbiota". *Microbiology and Molecular Biology Reviews* 81.4 (2017): e00036-17.

25. Victora CG., *et al*. "Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect". *Lancet* 387.10017 (2016): 475-490.

26. Yajnik CS., *et al*. "Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: The Pune Maternal Nutrition Study". *Diabetologia* 51.1 (2008): 29-38.

27. Feng Y., *et al*. "Regional antimicrobial resistance gene flow among the One Health sectors in China". *Microbiome* 13.1 (2025): 3.

28. Zhao Y., *et al*. "Global soil antibiotic resistance genes are associated with environmental drivers under a One Health framework". *Nature Communications* 16.1 (2025): 7141.

29. Indrio F., *et al*. "Epigenetic matters: The link between early nutrition, microbiome, and epigenome". *Frontiers in Pediatrics* 5 (2017): 178.

30. Gabbianelli R and Damiani E. "Nutri-epigenetics and gut microbiota: How birth care and nutrition influence the infant's epigenome". *International Journal of Molecular Sciences* 21.14 (2020): 5032.

31. Robertson RC., *et al*. "The gut microbiome and early-life growth in a population-based cohort from rural Zimbabwe". *Nature Communications* 14.1 (2023): 654.

32. Paul B., *et al*. "Influences of diet and the gut microbiome on epigenetic modulation in cancer and other diseases". *Clinical Epigenetics* 7 (2015): 112.

33. Neu J., *et al*. "Neonatal microbiome in the multiomics era: Development, function, and translational potential". *Pediatric Research* 98.4 (2025): 1223-1231.

34. Mitsis T., *et al*. "Influence of epigenetics and microbiota in early-life development: A possible role for exosomes". *International Journal of Epigenetics* 4 (2024): 3.

35. Linnér A and Almgren M. "Epigenetic programming - The important first 1000 days". *Acta Paediatrica* 109.3 (2020): 443-452.

36. Nohesara S., *et al*. "Maternal gut microbiome-mediated epigenetic regulation in neurodevelopment". *Nutrients* 16.24 (2024): 4355.

37. Hill CJ., *et al*. "Evolution of gut microbiota composition from birth to 24 weeks in the INFANTMET cohort". *Microbiome* 5.1 (2017): 4.

38. van Dijk SJ., *et al*. "Effect of prenatal DHA supplementation on the infant epigenome: results from a randomized controlled trial". *Clinical Epigenetics* 8 (2016): 114.

39. Koemel NA., *et al*. "Maternal dietary fatty acid composition and newborn epigenetic aging-a geometric framework approach". *American Journal of Clinical Nutrition* 115.1 (2022): 118-127.

40. Küpers LK., *et al*. "Maternal Mediterranean diet in pregnancy and newborn DNA methylation: a meta-analysis in the PACE Consortium". *Epigenetics* 17.11 (2022): 1419-1431.

41. Lee HS., *et al*. "Dietary supplementation with polyunsaturated fatty acid during pregnancy modulates DNA methylation at IGF2/H19 imprinted genes and growth of infants". *Physiological Genomics* 46.23 (2014): 851-857.

42. Monasso GS., *et al*. "Meta-analysis of EWAS on pregnancy vitamin B12 and offspring DNA methylation". *Epigenetics* 18.1 (2023): 2202835.

43. Joubert BR., *et al*. "Maternal plasma folate impacts differential DNA methylation in newborns". *Nature Communications* 7 (2016): 10577.

44. Hartwig FP., *et al*. "Association between breastfeeding and DNA methylation over the life course". *Nutrients* 12.11 (2020): 3309.

45. Sherwood WB., *et al*. "Epigenome-wide association study reveals duration of breastfeeding is associated with epigenetic differences in children". *International Journal of Environmental Research and Public Health* 17.10 (2020): 3569.

46. Briollais L., *et al*. "DNA methylation mediates the association between exclusive breastfeeding and BMI trajectories in early life". *Clinical Epigenetics* 13.1 (2021): 119.

47. Wampach L., *et al*. "Birth mode is associated with earliest strain-conferred gut microbiome functions". *Nature Communication* 9.1 (2018): 5094.

48. Mitchell CM., *et al*. "Delivery mode affects stability of early infant gut microbiota". *Cell Reports Medicine* 1.9 (2020): 100156.

49. Reznik SE., *et al*. "Effect of Cesarean delivery on the neonatal gut microbiome in an under-resourced Bronx population". *BMC Pediatrics* 24 (2024): 450.

50. Nguyen M., *et al*. "Impact of probiotic *Bifidobacterium infantis* EVC001 feeding in early infancy: microbiome and inflammation". *Frontiers in Pediatrics* 9 (2021): 618009.

51. Bajorek S., *et al*. "*Bifidobacterium infantis* EVC001 is well tolerated and improves HMO utilization in preterm infants". *Frontiers in Pediatrics* 9 (2022): 795970.

52. Sohn K., *et al*. "*Bifidobacterium infantis* EVC001 is associated with reduced necrotizing enterocolitis and improved feeding tolerance in premature infants". *Journal of Perinatology* 45.5 (2024): 635-641.

53. Masi AC., *et al*. "Human milk microbiota, oligosaccharide profiles, and infant gut microbiome in preterm infants diagnosed with necrotizing enterocolitis". *Cell Reports Medicine* 5.9 (2024): 101708.

54. Fan Y., *et al*. "Human milk oligosaccharide composition at 6 weeks and temperament and eating behaviors through 4 years". *Nutrients* 17.13 (2025): 2080.

55. Kenney AD., *et al*. "A review of human milk oligosaccharide concentrations of breast milk for infants and young children through 24 months of age". *Frontiers in Pediatrics* 13 (2025): 1649609.

56. Sato K., *et al*. "Absolute quantification of eight human milk oligosaccharides and associations with neurodevelopmental outcomes". *Journal of Food Science* 89.12 (2024): 10152-10170.

57. Mao S., *et al*. "Patterns of human milk oligosaccharides in mature milk are associated with infant gut microbiota". *Nutrients* 16.9 (2024): 1287.

58. Ryan FJ., *et al*. "*Bifidobacteria* support optimal infant vaccine responses". *Nature* 641.8062 (2025): 456-464.

59. Benitez AJ., *et al*. "Antibiotic exposure is associated with minimal gut microbiome perturbations in healthy term infants". *Microbiome* 13.1 (2025): 21.

60. Kiu R., *et al*. "Impact of early life antibiotic and probiotic treatment on gut microbiome and resistome of very-low-birth-weight preterm infants". *Nature Communications* 16.1 (2025): 7569.

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